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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,996	12/03/2001	William M. Partridge	407T-994110US	3004

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EXAMINER
WOLLENBERGER, LOUIS V

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
05/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/005,996	PARTRIDGE ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *4,26 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-25 and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Location of the Application

The location of the application has changed. The application has been docketed to Examiner Louis V. Wollenberger.

Status of the Application

1. Applicant's response filed 3/20/07 has been fully considered. Rejections and/or objections not reiterated from the previous office action mailed 7/27/05 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-31 are pending in this application. Claims 4, 26-27 remain withdrawn pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-3, 5-25, and 28-31 are currently under examination.

Claim Objections—new

Claim 24 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 24 indirectly depends from claim 20, which requires that the

antibody be a monoclonal antibody; thus, the "wherein" recitation of claim 24 requiring that the antibody be a monoclonal antibody does not further define the invention.

***

Claims 3, 5, and 25 are objected for reciting non-elected subject matter. Specifically, the claims recite non-elected targeting ligands such as substrates of receptors and antibodies targeted to molecules other than the insulin receptor, elected by applicants in their response filed on or about 5/21/04.

***

Claims 16 and 18 are objected to because of the following informalities:

Claim 16 includes the term "125˙I" Although it appears clear that the term is intended to mean radioactive 125-iodine, for clarity it is suggested that applicant amend the form to be consistent with that used in claim 17, for example.

Claim 18 recites a Markush-style group that is confusing in that the series of alternatives is interrupted by the conjunction "and" in front of "enzyme." It appears that "and" in this case was intended to be "an." The only "and" in the series should appear at the end to signify the final member.

Appropriate correction is required.

Claim Rejections - 35 USC § 112—withdrawn

2. The rejections of Claims 1 and 3 (and claims 2, 5-25 and 28-31, which depend directly or indirectly from claims 1 or 3) under 35 U.S.C. 112, second paragraph, as being indefinite are withdrawn in view of Applicants' amendment to the claims

Claim Rejections - 35 USC § 102—new

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 5-8, 11, 12, 14-16, 18, and 28-31 are rejected under 35 U.S.C. 102(b) as being anicipated by Pardridge et al. (WO 92/22332).

WO 92/22332 taught methods for making and intravenously administering radiolabeled, avidin-biotin-antisense oligonucleotide complexes to vertebrates for delivery into brain cells *in vivo* for both diagnostic and therapeutic purposes (see document throughout, for example, pp. 12-16). It is taught for example that the avidin-biotin technology may also be used in the diagnosis of disorders using standard imaging technology such as positron emission tomography or single photon computer emission tomography. For example, a radio-labelled cholecystokinin (CCK) peptide may be delivered to brain using the present invention for the purpose of imaging CCK-specific receptors in the diagnosis of mental disorders. Conversely, a radiolabeled antisense oligonucleotide may be delivered to tissues for the purpose of imaging cancer or viral disorders

(page 31). The antisense oligos may be directed to any mRNA in the cell, including any enzyme mRNA (page 12).

It is further taught that in addition to radioactive labeling of the antisense oligo (e.g., with 32-P), the avidin itself may be radiolabelled with 125-iodine and also be linked to a cell targeting moiety such as receptor ligands, such as but not restricted to insulin and transferrin, anti-receptor monoclonal antibodies, cationized proteins, and lectins (page 7-8).

The biotin-avidin group linked to the antisense oligo is said to act as a protection against nuclease degradation (page 12-13, 26-27).

Accordingly, Pardridge et al. (WO 92/22332) anticipates the instantly claimed invention.

Claim Rejections - 35 USC § 103—maintained

3. Claims 1-3, 5-25 and 28-31 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Penichet et al. 1999 (Reference 39, PTO-1449 filed 8/23/02, instant application) or Pardridge et al. 1995 (Reference 38, PTO-1449 filed 8/23/02, instant application) in view of Hnatowich 1999 (Reference 21, PTO-1449 filed 8/23/02, instant application), Kurihara et al. 1999 (Reference 27, PTO-1449 filed 8/23/02, instant application), Tavitian (1998, Reference 48, PTO-1449 filed 8/23/02, instant application) and Zhao (Reference 59, PTO-1449 filed 8/23/02, instant application) for the reasons of record.

Response to Arguments

Applicants argue the combined art offers no reasonable expectation of success that the construct recited in the present claims could cross the BBB, cross the CM, bind a target nucleic

acid, and be detectable, and that the Examiner improperly argues that Penichet et al. and Pardridge et al. disclose constructs that inherently perform the claimed method (Remarks, page 9). Applicants argue obviousness cannot be predicated on what is unknown.

Applicants argue the references individually, stating that Penichet et al. and Pardridge et al. do not teach that the radiolabeled, antibody conjugated antisense nucleic acid actually enters a brain cell in sufficient quantity to detect gene expression or that it hybridizes with any nucleic acid therein. Applicants argue Penichet et al. constitutes a teaching away as it analyzes solubilized brain cells instead of intact brain cells. Applicants assert that because no mention of hybridization to a transcript in the cell was made, the references do not provide a reasonable expectation of success.

Applicants continue to argue the references individually asserting that Kurihara, Hnatowich, and Tavitian et al. provide no reasonable expectation of success.

Applicant's arguments filed 3/20/2007 have been fully considered but are not persuasive.

Contrary to Applicants assertions, the motivation or reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed is not predicated on unknown or unrecognized properties. The reason to combine is predicated on the fact that the prior art, as exemplified by the combination of references cited, taught and suggested making and using a variety of diagnostic materials, including conventional as well as peptide antisense nucleic acids, comprising radialabels and antibody conjugates, for *in vivo* assays, including gene expression analysis, in intact brain cells in animals.

Applicants will note that products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable.

Therefore, if the prior art teaches and/or suggests the identical chemical structure, the properties applicant discloses and/or claims are necessarily present.

Additionally, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." MPEP §2112.01.

Applicant provides no evidence to show the absence of specific properties.

Finally, it is not necessary that the prior art recognize or teach any or all inherent properties or advantages of a compound, so long as the prior art provides some reason for making and using the compound in the claimed method. MPEP §2112 and 2145.

In the instant case, the prior art taught and suggested each of the material limitations and steps recited in the instant claims. Applicants have not specifically argued otherwise.

The motivation or reason to combine is not based on an inherent feature but on the teachings of the prior art which taught materials and methods for detecting, measuring, and inhibiting gene expression vivo in brain cells. This is sufficient motivation to make and use the instant method. It is not necessary for the prior art to confirm or identify inherent properties since these properties are presumed to be intrinsic. It is Applicants' burden to show they do not exist. Such evidence, however, if directed against materials specifically recited in encompassed by the instant claims, would tend to cast doubt on the objective truth of the statements in Applicants' own application.

Rather, Applicants appear to argue that because the prior art cited herein did not verify or confirm certain inherent properties, such as transport into brain cells, hybridization of complementary nucleic acids, and identification of detectable quantities of labeled antisense in brain cells, the prior art provided no reasonable expectation of success. The Examiner disagrees. While difficulties and challenges are present in any in vivo application, the prior art provided the necessary tools and methods for imaging radiolabelled antisense DNAs in a variety of tissues, including the brain, as evidenced by Hanatowich, who discusses the state of the art with regard to the use of 11-indium labeled antisense and nuclear medicine, as well as important proof-of-principle examples.

Further, there is no indication that one of skill would have been deterred from using antisense-based nucleic acids to detect and quantify gene expression in brain cells based on the prior art cited. Rather the prior art encourages one of skill to focus on the use of ligand targeted, radiolabelled antisense nucleic acids for in vivo imaging, as evidenced by Hnatowich for example.

The fact that Penichet et al. used a solubilization technique instead of imaging would not dissuade one of skill from pursuing the use of the claimed materials in the manner suggested by the prior art (Hnatowich for example). Additionally, Applicants provide no evidence that the method uses by Penichet et al. did not in fact result in delivery and uptake by the cells.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The instant rejection is not relied

on for what any one reference alone taught and suggested, but what the combination of references as a whole explicitly and implicitly suggested to one of skill at the time of invention.

Accordingly, the instant claims remain rejected fro the reasons of record.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LVW
Art Unit 1635
May 3, 2007

SEAN MCGARRY
PRIMARY EXAMINER
AU 1635